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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,668	04/14/2006	Frank-Christophe Lintz	65177(45107)	1828

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EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,668	LINTZ ET AL.	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Amendments and Remarks filed on 10/03/07. Claims 50, 51, 52 and 55 have been amended and no claims have been cancelled or newly added. Accordingly claims **25-55** remain pending.

Claim Rejections - 35 USC § 112

The rejection of claims 50-55 under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention, has been withdrawn due to amendments to the said claims.

The rejection of claim 46 as being indefinite for reciting "eFlow™ type of PARI" has been withdrawn due to arguments and a showing on the record that the said device is well known.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25-26, 29-30, 35-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005).

Malvolti et al teach optimized formulations of tobramycin for aerosolization in the form of additive-free, **isotonic solution** whose pH has been optimized to ensure adequate shelf-life at room temperature. Said formulation can be advantageously used

for treatment and prophylaxis of acute and chronic endobronchial infections (see abstract). In a preferred embodiment a formulation is prepared containing 300 mg of tobramycin sulfate in 4 ml of half-saline aqueous solution (0.45% of sodium chloride) in order to have an osmolarity ranging from 280 to 350 mOsm/l and it has a pH between 4.0 and 5.5 (page 5, line 25 to page 6, line 3). Other formulations have been prepared using **¼ normal saline** (see page 7). Malvolti et al disclose that the inventors of the patent EP 734249, it was discovered that "a further advantage of a **quarter normal saline**, i.e. saline containing 0.225% of sodium chloride with 60 mg/ml tobramycin is that this formulation is **more** efficiently nebulised by an ultrasonic nebuliser *compared* to tobramycin formulated in a solution of 0.9% normal saline (page 7, lines 11-15).

Malvolti et al also disclose a method of preparing the said formulations which includes the steps of adjusting the pH by adding an acid adjuvant such as sulfuric acid and also sterile filtering the solution (see pages 9-10). The prepared formulations are typically distributed in 2 ml polyethylene colorless unit dose vials under nitrogen purging (page 11, lines 11-12) and are administered by a nebulizer such as a jet PARI nebulizer (see page 14).

Tables 1 and 2 show a formulation that comprises between 67.5 and 82.5 mg/ml tobramycin.

Malvolti et al does not anticipate the claims because it does not disclose a formulation that contains 2 mg/ml sodium chloride or less, however it does disclose using ¼ normal saline and it is disclosed that lower concentrations of sodium chloride in

the said solution formulation are beneficial, thus one of ordinary skill in the art would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation. In other words, the claims would have been obvious because a person of ordinary skill has good reason within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Furthermore, Malvolti lacks certain specifics of the claimed nebulizer or packaging such as closure elements and nose pieces, however it is considered while the said limitations are not expressly disclosed, they exist in the jet or ultrasonic nebulizers and packages disclosed by the prior art. It is also noted that the instant claims are drawn to "a sterile liquid preparation" and the packaging or mode of administration are not patentable elements of a formulation.

Claims 25-26, 29-30, 36-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Montgomery (6,083,922).

Montgomery teach a method of treating chronic tuberculosis using a preservative-free concentrated tobramycin aerosol formulation delivering tobramycin to the lung endobronchial space (see abstract). The formulations for use in the said methods comprise from 40 to 800 mg of tobramycin in 5 ml of quarter normal saline. This corresponds to 8-160 mg/ml (col. 10, lines 9-17). The tobramycin formulations comprising 60 mg/ml of ¼ **NS** have an osmolarity in the range of 165-190 mOsm/l (col. 10, lines 52-55). The pH is between 5.5 and 7.0 (col. 10, lines 60-67).

Montgomery discloses that the formulations are administered by nebulizers such as jet and ultrasonic nebulizers. A jet nebulizer works by air pressure and an ultrasonic nebulizer works by piezoelectric crystal. Examples of the said nebulizers include Pari LC and Pari LC plus (see col. 12, lines 1-59). Examples 1-3 disclose the ingredients and amounts of the formulations. Other than tobramycin and saline, sulfuric acid is present. Montgomery also states that "Higher amounts of tobramycin was delivered when tobramycin was formulated in ¼ **diluted saline** than tobramycin formulated in *full strength nondiluted saline"* (see col. 16, lines 17-19). The formulation is stored in polyethylene LDPE vials in foil overpouch (col. 16, lines 60-65).

Montgomery does not anticipate the claims because it does not disclose a formulation that contains 2 mg/ml sodium chloride or less, however it does disclose using ¼ normal saline and that ¼ **normal saline is advantageous** because it allows for higher amounts of tobramycin being delivered, thus it would have been clear to one of ordinary skill in the art that lower concentrations of sodium chloride in the said solution formulation would be beneficial. One of ordinary skill would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation for aerosol administration.

Claims 27-28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005) as applied to claims 25-26, 29-30, 35-55 above, and further in view of Wiedmann et al (5,747,001).

Malvolti et al, discussed above lacks specific disclosure on adding isotonising agents and surface active adjuvants.

Wiedmann et al teaches an aerosol comprising droplets of an aqueous dispersion of nanoparticles, comprising an active agent having a surface modifier on the surface thereof (see abstract). The said modifiers include calcium stearate, magnesium aluminum silicate, lecithin (phosphatides) and tyloxapol (see cols. 3-4). The said aerosols are typically administered by nebulizers such as jet and ultrasonic nebulizers (see col. 3, lines 17-28).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the formulations of Malvolti et al by adding the surface modifiers as taught by Wiedmann et al with a reasonable expectations of successfully preparing formulations for inhalation that are stable and easy to flow.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al (WO 03004005) as applied to claims 25-26, 29-30, 35-55 above, and further in view of Azria et al (5,759,565).

Malvalti et al, discussed above, lacks specific disclosure on viscosity of the formulations.

Azria et al teach pharmaceutical compositions for nasal administration, comprising an active and a surfactant in a liquid carrier. The said compositions should possess appropriate isotonicity and viscosity. The preferred osmotic pressure is from about 260 to about 380 mOsm and the viscosity is from about 2 to about $4x10^{-3}$ Pa.S (see col. 4, lines 5-30).

It would have been obvious to one of ordinary skill in the art at the time the invention was made given the general formulations of Malvolti et al on nebulizer solution formulations comprising an active agent and surfactants to have looked in the art for suitable and appropriate isotonicity and viscosity for the formulations as taught by Azria to prepare and effectively deliver a solution formulation to the mucosa for maximum absorption and systemic distribution.

Response to Arguments

Applicant's arguments filed 10/03/07 have been fully considered but they are not persuasive.

With regards to the rejections of claims under 35 U.S.C. §103(a), Applicant argues that the primary references, Malvolti et al and Montgomery do not teach or suggest the limitations as claimed. Specifically, Applicant argues that neither references discloses "a sterile, liquid preparation in the form of an aqueous solution for the application as a solution for injection or as an aerosol containing about 80 mg/ml to 120 mg/ml of tobramycin and an acidic adjuvant, wherein the preparation comprises not

more than 2 mg/ml of sodium chloride".

Applicant states that "Examiner concludes that it would have been clear to one of ordinary skill in the art that lower concentrations of sodium chloride in the said solution formulation would be beneficial, thus one of ordinary skill would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation" (regarding the Malvolti reference) and "[o]ne of ordinary skill would have been able to optimize the concentration ranges of tobramycin and sodium chloride to prepare a more effective formulation for aerosol administration" (regarding the Montgomery reference), the Office Action fails to articulate a reason or rationale to support this conclusion. That is, the Examiner has failed to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed". This is not persuasive because it has clearly been shown that one of ordinary skill in the art, given the disclosures of Malvolti et al and Montgomery, would be able to optimize the concentrations of sodium chloride. Malvolti discloses that it was discovered that lower concentrations of sodium chloride, meaning ¼ normal saline provides formulations that are MORE efficiently nebulized. Montgomery discloses that HIGHER amount of tobramycin was delivered when tobramycin was formulated in ¼ normal saline than in full strength saline (see Example 2 and Table 4). It is considered that adequate motivation has been given to one of ordinary skill in the art, by the said references, to make and use the invention as claimed. In other words, it is disclosed that lower concentrations of sodium chloride are advantageous in formulating solutions

of tobramycin. Thus one of ordinary skill would be able to try formulations comprising a lower concentration of sodium chloride than ¼ normal saline.

Applicant further argues that "nothing in the prior art teaches or suggests that the lowering of the sodium chloride concentration would result in a less irritating and more compatible formulation. In the absence of such a suggestion, it is improper to conclude that the invention according to the main claim would have been obvious in view of either of Malvolti et al. or Montgomery alone or even a combination thereof. This is not commensurate with the scope of claims. The instant claims are drawn to a "saline preparation" and "a method of treating a disorder". The limitations of "less irritating and more compatible" have not been recited and would be irrelevant because that would be a non-patentable limitation in a formulation or method claim. In other words, the motivation to alter the concentration range of sodium chloride comes form the prior art and regardless of whether it is the same or different than the motivation inventors had, it is a motivation and adequate to meet the limitations of the instant claims.

Applicant also argues against the combination of references and states that "one of skill in the art would not be motivated to combine the teachings of either Malvolti et al. or Montgomery et al. with any prior art so as to successfully arrive at the invention as described in the instant claims because none of Malvolti et al., Montgomery et al., the prior art or combinations thereof, teach or suggest these essential elements of the claims". This is not persuasive because it has been established that there is adequate motivation provided by the Malvolti et al and Montgomery references to lower the concentration of sodium chloride for improvements as noted above. The secondary

references were brought in merely to show that the limitations missing in the primary references were known in the art and that their combinations would have been obvious to one of ordinary skill in the art. In response to applicant's arguments that there is no specific suggestion or teaching in the references to combine prior art, it is noted that KSR forecloses the argument that specific teaching, suggestion or motivation is required to support a finding of obviousness (see *Ex parte Smith*,--USPQ2d--, slip op. at 20) (KSR, 82 USPQ2d at 1396).

Applicant's arguments are further not persuasive because they amount to a general allegation that the claims define a patentable invention without showing any criticality of a formulation comprising "not more than 2mg/ml of sodium chloride". Simply stating that the prior art does not teach or suggest that lowering of sodium chloride concentration would result in a less irritating and more compatible formulation is not grounds for novelty or non-obviousness. It is further noted that neither the specification nor the response provides any data comparing the formulations and their effectiveness. Table 1 of specification (page 16) attempts to compare a formulation according to Example 6 with commercially available formulation TOBI® 300 mg (containing 2.25 mg/ml Nacl). Firstly, the devices used for their administration are different and most of the properties compared appear to be more a function of the device than the formulation. Secondly, the data provided is not related to the concentration of sodium chloride and is inconsistent. For example the delivery dose in mg shows that TOBI® performs better, while the delivery dose in % of the dose shows instant formulation performs better.

In summary, the instant claims are met by the references on the record. The only difference between instant formulations and formulations disclosed by the Malvolti et al or Montgomery references is the concentration of sodium chloride. It has been shown that both references provide adequate motivation to one of ordinary skill in the art to alter the concentration of sodium chloride to improve nebulization and to deliver higher amount of medicament (tobramycin).

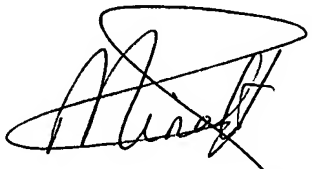
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Mina Haghighatian
Patent Examiner
December 12, 2007